ORIGINAL RESEARCH

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Development of a sensitive prognostic scoring system for the evaluation of severity of acute-on-chronic hepatitis B liver failure: A retrospective cohort study

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Abstract

Purpose: The purpose of the current study was to establish an objective, simple, and sensitive prognostic scoring system for estimating the severity of acute-on-chronic liver failure in hepatitis B (ACLFB).

Methods: A novel prognostic scoring system was calculated from six clinical indices including total bilirubin (TB), prothrombin activity (PTA), creatinine (Cr), hepatic encephalopathy (HE), infections, and the depth of ascites from 726 patients with ACLFB. Indices were scored from 1 to 4 according to their severity. Groups of the same patients were scored with three-indices (TB, PTA and Cr), four-indices (TB, PTA, Cr and HE), five-indices (TB, PTA, Cr, HE and the depth of ascites) or six-indices (TB, PTA, Cr, HE, the depth of ascites, and infections). The differences in the sensitivity and specificity of four scoring systems were analyzed.

Results: The demarcation points of the three-, four-, five- and six-indices scoring systems were 4.62, 6.12, 7.88 and 9.57, respectively. The analysis of the areas under the receiver operating characteristic (ROC) curve indicated that the four-, five- and six-indices scoring systems were more exact, and objective than the three-indices prognostic scoring system. In the six-indices scoring system, the survival rates of patients with scores from 2 to 6 was 98.31% (233/237), and the mortality rate of patients with scores of 16 and above was 100.00% (140/140), while the mortality rates were 8.33% (3/36) and 96.43% (27/28) for those with scores from 7 to 15, respectively.

Conclusion: A six-indices scoring system is an objective, pertinent, and sensitive system, and may be useful for the prognostic evaluation of ACLFB.

Manuscript submitted 6th October, 2011
Manuscript accepted 29th January, 2012

Clin Invest Med 2012; 35 (2): E75-E85.

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The therapy for acute-on-chronic liver failure in hepatitis B (ACLFB) includes a variety of medical treatments such as nucleoside analog therapy [4,5,6,7] and bioartificial liver devices [7,8]. Despite these treatments, the mortality of hepatic failure remains high [10,11]. Recent studies have indicated that orthotopic liver transplantation is the treatment of choice for patients with end-stage liver disease including ACLFB [7]; however, liver transplantation has limitations including a lack of readily available donors, immune rejection [1,2,9,10] and recurring viral infection [3,11,12,13]. Therefore, predicting the severity and prognosis of patients with ACLFB is very important and an early and accurate prognostic assessment is critically important for selecting the optimal treatment pathway. Accordingly, a number of prognostic models have been proposed to aid in decision-making for patients with ACLFB to be treated either pharmaceutically or by liver transplantation. The well-accepted prognostic models, including the King's College Hospital (KCH) [14] criteria and the model for end-stage liver disease (MELD) [4] score, all possess drawbacks for the prognostic evaluation of ACLFB. Therefore, our study was aimed at establishing an objective, simple, sensitive, and clinically useful prognostic scoring model for estimating the severity of ACLFB.

Methods and Patients

Patients

Retrospective cohort that included 726 hospitalized patients (635 men, 91 women; mean age, 43.5 ± 11.6 years) with ACLFB were recruited from the Department of Infectious Diseases, The Third Affiliated Hospital, Sun Yat-Sen University, China, between January 2003 and September 2009. They were divided into two groups: a survival group including 355 patients, and a deceased group including 371 patients. The inclusion criteria were: ACLFB, defined as an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with chronic HBV infection according to consensus recommendations of the Asian Pacific Association for the Study of the Liver in 2009 [21]. The exclusion criteria were: co-infection with other viruses (HIV), other causes of chronic liver failure, co-existing hepatocellular carcinoma (HCC), portal vein thrombosis, renal impairment, and pregnancy. The study was performed according to the World Medical Association Declaration of Helsinki, and the protocol was approved by the local medical ethics committee of The Third Affiliated Hospital of Sun Yat-Sen University. Written informed

consent was obtained from all individuals included in this study.

General Management of Patients

The 726 patients were given standard medical treatment [3] including intravenous antibiotics, high calorie diet (35-40 cal/kg/day), lactulose, bowel enemas, and intensive care monitoring. Patients also received albumin, terlipressin, anti-viral therapies, and proton pump inhibitors, if required, or plasma exchange. Orthotopic liver transplantation was not adopted mainly due to the cost and lack of available donors. All patients had obvious clinical endpoints, ie survival or death.

Baseline Assessment of Patients

Retrospectively collected data included patient demographics, clinical, laboratory variables including virological tests, upper gastrointestinal (GI) endoscopy and abdominal ultrasound. The severity of the liver disease was assessed by MELD scoring. For the diagnosis of HBV, serological tests for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), immunoglobulin M (IgM) anti-HBc, total anti-HBc, and anti-HBe were done by commercially available enzyme-linked immunoassays. HBV DNA estimation was done with the real-time polymerase chain reaction (PCR) method (lower limit of detection 50 IU/mL, Roche Taqman assay).

Development of a Novel Prognostic Scoring System to predict the severity of acute-on-chronic liver failure in hepatitis B

A novel scoring system was developed from six clinical indices including PTA, TB, Cr, HE, presence of infections, and the maximum depth of ascites or pleural fluid (detected by ultrasound B). Scores were assigned from 1 to 4, according to their severity, to provide a total score. The patients with ACLFB were evaluated for the peak of disease severity in the survival group, and those patients with ACLFB were evaluated if they appeared moribund in the deceased group. Groups of patients were scored with three indices (TB, PTA and Cr), four indices (TB, PTA, Cr and HE), five indices (TB, PTA, Cr, HE and the depth of ascites) or six indices (TB, PTA, Cr, HE, the depth of ascites, and the presence of infections). The new prognostic scoring system is described in detail in Table 1. Differences in the sensitivity, specificity and practicality of four scoring systems were analyzed.

TABLE 1. Assigned scores of novel scoring system

Indices	Assigned Scores				
	0	1	2	3	4 scores
Total bilirubin ($\mu\text{mol/L}$)	$x < 10 \text{ ULN}$	$10 \leq x < 20 \text{ ULN}$	$20 \leq x < 30 \text{ ULN}$	$30 \leq x < 40 \text{ ULN}$	$x \geq 40 \text{ ULN}$
Creatinine ($\mu\text{mol/L}$)	Normal	$1.0 < x < 1.1 \text{ ULN}$	$1.1 \leq x < 1.2 \text{ ULN}$	$1.2 \leq x < 1.3 \text{ ULN}$	$x \geq 1.3 \text{ ULN}$
Activity of PT (%)	$x \geq 40$	$30 \leq x < 40$	$20 \leq x < 30$	$10 \leq x < 20$	$x < 10$
HE (Stage)	None	I	II	III	IV
The maximum depth of ascites (mm)	None	$0 > x < 40$	$40 \leq x < 80$	$x \geq 80$	$x \geq 80$ + one or uni- bilateral pleural effusion
WBC $\times 10^9/\text{L}$)	Normal	$x \leq \sim < 15$ or $70\% < x < 80\%$	$15 \leq x < 20$ or N $80\% < x < 90\%$	$x \geq 20$ or $N > 90\%$	inflammation of lung

0-3 scores depend on WBC $10^9/\text{L}$ or N%; 4 scores calculated if only Inflammation manifestation of lung – Images.

Abbreviations: WBC, white blood cell; ULN, upper limit of normal; N, neutrophil; PT, prothrombin time; HE, hepatic encephalopathy.

TABLE 2. Baseline characteristics of included patients on admission

Parameters	Deceased group (n=371)	Survival group (n=355)	t/ χ^2 -value	P-value
Age (yr)	46.0 $\pm$ 10.3	44.7 $\pm$ 8.7	1.83	0.07
Males (%)	337 (90.84)	316 (89.01)	1.63	0.20
WBC ($\times 10^9/\text{L}$)	7.71 $\pm$ 3.47	7.48 $\pm$ 4.32	0.79	0.43
Hb ($\times \text{g/L}$)	129.35 $\pm$ 11.5	130.23 $\pm$ 14.1	0.92	0.36
Platelet ($\times 10^9/\text{L}$)	97.67 $\pm$ 38.38	149.54 $\pm$ 67.90	12.70	<0.001
ALT (U/L)	681.27 $\pm$ 459.26	738.31 $\pm$ 604.16	1.44	0.15
Albumin (g/L)	32.15 $\pm$ 2.95	32.07 $\pm$ 2.79	0.38	0.70
TB ($\mu\text{mol/L}$)	469.65 $\pm$ 219.86	435.59 $\pm$ 216.13	2.1	0.35
PT (sec)	22.98 $\pm$ 4.9	22.65 $\pm$ 5.95	0.82	0.41
PTA (%)	31.90 $\pm$ 9.170	30.97 $\pm$ 9.31	1.36	0.18
INR	2.33 $\pm$ 0.587	2.26 $\pm$ 0.63	1.55	0.12
Cholinesterase (U/L)	4495.17 $\pm$ 2047.30	4478.11 $\pm$ 1387.16	0.13	0.89
AFP ($\mu\text{g/L}$)	206.78 $\pm$ 314.87	184.23 $\pm$ 253.21	1.06	0.28
HBVDNA (log ₁₀ copies/ml)	6.07 $\pm$ 1.76	5.45 $\pm$ 1.56	5.01	<0.001
Encephalopathy (%)	122(32.88)	129 (36.48)	0.96	0.33
HRS (%)	35(9.43)	20 (5.63)	3.74	0.06
SBP (%)	232(62.53)	186 (52.39)	7.63	0.06
Ascites (%)	284(76.55)	246 (69.29)	4.84	0.03
MELD score	21.73 $\pm$ 5.97	20.98 $\pm$ 5.61	1.74	0.08

All values are expressed as mean $\pm$ SD or median and interquartile range, and category values are described by count and proportions.

Abbreviations: WBC white blood cells; Hb Hemoglobin; ALT alanine aminotransferase; TB Total Bilirubin; PT prothrombin time; PTA prothrombin activity; INR international normalized ratio; AFP α -fetoprotein; HBV hepatitis B virus; HRS hepatorenal syndrome; SBP spontaneous bacterial peritonitis.

Demarcation points and ranges in scores of novel scoring system between survival and deceased groups

Demarcation points were calculated according to the following formula: the mean of scores in the deceased group – the mean of scores in the survival group = $\chi \times$ standard deviation in the deceased group + $\chi \times$ standard deviation in the survival group according to the statistics. Substituting the corresponding

scores into this formula resulted in the demarcation points and ranges in scores of the three-, four-, five-, and six- indices scoring systems between the survival and deceased groups. The use of a standard normal distribution graph of the statistics [24], and the value of χ as used in the above formula, resulted in the demarcation points and ranges in scores of above various scoring systems between the survival and deceased groups.

Statistical analysis

All data are expressed as means $\pm$ SD. Data analysis was performed using SPSS16.0 software. Analysis of predictive values of all scoring systems was performed using ROC curves, and for all analyses a P value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics in both the patient groups were similar (Table 2). The mean age was 46.0 ± 10.3 years in the deceased group and 44.7 ± 8.7 years in survival group. The patients were predominantly men (89.94%). There were 355 patients who died in the 3-month follow-up period (48.89%). The HBV DNA levels in the deceased group (6.07 ± 1.76 log 10 copies/ml) were significantly higher than those in survival group (5.45 ± 1.56 log 10 copies/ml, $P < 0.001$). Among the ACLFB patients, platelet counts in deceased patients ($97.67 \pm 38.38 \times 10^9/L$) were significantly lower than those in survival patients ($149.54 \pm 67.90 \times 10^9/L$, $P < 0.001$). Patients who survived had a lower ascites positivity rate (69.29% vs 76.55%; $P = 0.03$). Other baseline characteristics in both the patient groups were similar. The most common complication of ACLFB was spontaneous bacterial peritonitis (SBP) (418 patients; 57.58%), hepatorenal syndrome (HRS) (55 patients; 7.58%), and hepatic encephalopathy (251 patients; 34.57%).

Scores in each of the clinical indices of patients using the multi-indices scoring systems

Scores in each of the individual clinical indices in the deceased group were higher than those in the survival group in the 6-indices scoring system ($P < 0.001$) (Table 3).

The demarcation points and range of scores between the survival and deceased groups.

The demarcation points and range of scores in the four different scoring systems were compared between the survival and the deceased groups. The demarcation points in scores of the three-, four-, five- and six- indices scoring systems between the survival and the deceased groups were located at score of 4.57, 6.07, 7.82 and 9.50, respectively (Fig. 3. A, B, C, D). Score ranges of 66.29% patients in the deceased group and survival group were from 4.57 to 9.08 scores, and from 1.78 to 4.57 scores by three-indices scoring system. The score range of 84.44% of the patients in the deceased and survival groups were from 6.07 to 13.52 scores and from 1.05 to 6.07 scores by four-indices scoring system. Score ranges of 82.30% of the patients in the deceased and survival groups were from 7.82 to 15.79 scores and from 2.00 to 7.82 scores by the five-indices scoring system. Score ranges of 81.98% of the patients in the deceased and survival groups were from 9.57 to 18.73 scores and from 2.0 to 9.57 scores by the six-indices scoring system according to a normal statistical distribution (Table 4).

TABLE 3. Scores of clinical indices in groups.

	Survival (n=355)	Deceased (n=371)	t value	χ^2 value	p value
Total Bilirubin ($\mu\text{mol/L}$)	454.53 ± 175.64	604.43 ± 208.10	48.76		0.000
Total bilirubin scores	1.46 ± 0.82	2.08 ± 0.91	33.58		0.000
Activity of PT (%)	27.92 ± 7.12	17.71 ± 8.27	41.25		0.000
Activity of PT scores	1.71 ± 0.71	2.67 ± 0.85	43.74		0.000
Serum creatinine ($\mu\text{mol/L}$)	69.60 ± 36.34	206.49 ± 195.27	36.09		0.000
Creatinine scores	0.170 ± 0.73	2.09 ± 1.91	4.31		0.000
HE incidence (%)	22.82% (81/355)	90.57% (336/371)		340.61	0.000
HE scores	0.41 ± 0.83	2.98 ± 1.31	9.31		0.000
Infection (WBC $10^9/L$)	6.91 ± 3.59	12.79 ± 7.54	36.29		0.000
Neutrophil (%)	0.31 ± 0.32	0.76 ± 0.11	17.73		0.000
Infection scores	0.84 ± 1.23	2.32 ± 1.45	12.29		0.000
Incidence in lung (%)	11.83% (42/355)	36.12% (134/371)		58.268	0.000
Maximum depth of ascites (mm)	38.28 ± 34.97	57.44 ± 37.63	20.63		0.000
Ascites scores	1.35 ± 1.17	2.01 ± 1.14	21.89		0.000

Each of the clinical indices and their scores for patients in deceased group were higher than that in survival group in our new scoring system ($P < 0.001$).

Abbreviations: HE hepatic encephalopathy, PT prothrombin time.

TABLE 4. Percentage of demarcation points between survival group and deceased group using Three- to six-indices scoring systems.

Scoring System	Demarcation point	Ranges in scores	
		Deceased group	Survival group
Three-Indices	66.29%**	4.57-9.08	1.78-4.57
Four-Indices	84.44%	6.07-13.52	1.05-6.07
Five-Indices	82.30%	7.82-15.79	2.00-7.82
Six-Indices	81.98%*	9.57-18.73	2.0-9.57

**P<0.05 compared with four-, five-, and six-indices scoring systems, respectively; *P>0.05 compared to five- and four-indices scoring systems.

Abbreviations: T, total bilirubin; C, creatinine; P, prothrombin time; H, hepatic encephalopathy.

The survival rate and mortality rates of patients with ACLFB in the three-, four-, five-, and six-indices scoring systems

The survival and mortality rates of patients with ACLFB in the three-, four-, five-, and six-indices scoring systems are shown in Fig. 1A, B and 2A, B, respectively. Using the six-indices scoring system, the mortality rate of 237 patients, whose scores ranged from 2 to 6, was 98.31%, and there were only four deaths in all these patients. The mortality rate of patients whose scores were 16 or above was 100.00% (140/140). None of these patients survived. The mortality rate of 349 patients whose scores ranged from 7 to 15 was 65.04%. There were 122 survivor patients in the follow-up period. The mortality rate was 8.33% for patients whose score was 7, and 96.43% for patients whose score was 15. Thus, there was 10% increase in mortality rate for every 1-point increase in severity score. When the severity scores increased to a value of 8 in the six-indices scoring system, it was considered that there was a possibility of continued worsening of the condition, and prompt liver transplantation should be considered.

The performance including sensitivity and specificity of the three-, four-, five-, and six-indices scoring systems compared with each other

The results from Fig. 4 shows that the c-statistic of patients for the three-, four-, five-, and six-indices scoring systems were 0.900, 0.970, 0.967, and 0.963, respectively. Four scoring systems were all suitable ways to correctly predict the severity and prognosis of patients with ACLFB. The four- and six-indices scoring systems are objective, pertinent and sensitive, and are applicable for the prognostic evaluation of ACLFB with greater sensitivity than other two scoring systems.

Discussion

Despite all available treatments including medical treatment and bioartificial liver devices [6] for ACLFB, the mortality of ACLFB is more than 70% [9,10]. Until now, liver transplantation was considered to be the treatment of choice for patients with end-stage liver diseases, including ACLFB [7,17]. Predicting the severity and prognosis of patients with ACLFB who are been given general medical treatment is very important for these patients who might be candidates for liver transplantation. Therefore, it is necessary to develop an objective and simple system for making appropriate clinical decisions. Liver transplantation has limitations due mainly to a lack of donors [2]. For this reason, patients with liver transplants were not recruited into the current study, and our retrospective cohort included 726 patients with ACLFB who were only given standard medical treatments. Our study showed that the current novel prognostic scoring system may be of value in predicting the severity of patients with ACLFB, and may allow optimal therapeutic measures to be undertaken rapidly. Previous studies have shown that the liver has many complicated physiological functions. Therefore, a single index of liver function cannot estimate exactly the severity and prognosis of ACLFB. Comprehensive clinical indices have been used to evaluate the prognosis of liver failure worldwide. MELD [4] has been shown to be useful in determining the priority for the transplant waiting list for patients with end-stage liver disease; however, the range of MELD scores is too wide to be useful in predicting patient death risk due to end-stage liver disease [7]. In addition, MELD was based on only three indices; creatinine, bilirubin and international normalized ratio (INR). Prothrombin time (PT) is a universal indicator of liver disease severity. PT is expressed in seconds, ratio, activity percentage, i.e., prothrombin activity (PTA), and is standardized based on the INR. INR is calculated as follows: $INR = (PT \text{ ratio})^{ISI}$, where ISI is the International Sensitivity Index of the thromboplastin reagent used. There are differences between PTA and INR: in patients with liver failure, only PTA expression was found to eliminate variability in PT results obtained with the various thromboplastins, while INR, expressed as ratios, remained significantly different. Previous studies have suggested that in patients with liver failure, the use of INR provides inadequate standardization, and that only PT expressed in terms of PTA may provide a universal solution to the problem of variability in thromboplastin sensitivity [23]. Moreover, the calculation of MELD is too complicated and is not easily used clinically. The calculation of MELD scores depends on the Malinchoc formula and requires a calculator or computer. The prognostic scoring system described in this study represents a simpler and therefore

Fig1

A

B

FIGURE 1. A. Survival and mortality rates of patients with ACLFB using three-indices scoring system. B. Survival rate and mortality rate of patients with ACLFB using four-indices scoring system.

Fig 2

FIGURE 2. A. Survival rate and mortality rate of patients with ACLFB using five-indices scoring system. B. Survival rate and mortality rate of patients with ACLFB using six-indices scoring system.

FIGURE 3. The demarcation points and ranges in scores of three- (A), four- (B), five- (C), and six-indices scoring systems (D) between the survival group and the deceased group.

FIGURE 4. ROC curves of four different scoring systems. C-statistic of patients with three-, four-, five-, and six-indices scoring systems was 0.900 (95% C value confidence interval from 0.878 to 0.922), 0.970 (95% C value confidence interval from 0.959-0.981), 0.967 (95% C value confidence interval from 0.956-0.977), and 0.963 (95% C value confidence interval from 0.956-0.977), respectively.

more convenient scoring system for clinicians in comparison with MELD.

A second index, King's College Hospital criteria (London's criteria) [14], is able to predict the severity of non-acetaminophen-induced fulminant hepatic failure, and the positive predictive value and negative predictive value; however, the predictive accuracy of these criteria is only 79%, 50%, and 68% [16], respectively.

Takahashi *et al.* [15] performed a multicenter study showing that their risk of death indices were able to assess the severity of fulminant in hepatitis B, and were superior to London's criteria for preoperative evaluation of liver transplantation; however, it was inferior to MELD in terms of sensitivity and specificity, since the sensitivity was only 0.83 and the specificity 0.77.

Clinical manifestations of ACLFB include hyperbilirubinemia, decreased prothrombin time activity, encephalopathy, hepatorenal syndrome [11,18] and ascites. ACLFB often follows chronic hepatitis B or cirrhosis. Peripheral leucocytosis in patients with chronic hepatitis complicated by infection will increase; however, peripheral leucocytes in patients with cirrhosis complicated by infection may not increase. Therefore, assessment of infection scores depends on the condition of WBC $10^9/L$ or N%, which meets score standards early. The range of total scores was from 2 to 24. The four-, five-, and six-indices scoring systems were superior in both specificity and sensitivity for predicting the severity of ACLFB compared with the three-indices system, mainly because the three-indices system did not include main liver function indices as did the MELD score [19]. Ascites and infection indices were added to

produce the six-indice scoring system, but those additions did improve the specificity or sensitivity.

Our previous study [20] showed there was an overlap between confidence intervals in the MELD scoring system. In the six-indices scoring system, there is no overlap between confidence intervals. Therefore, when the severity of ACLFB exceeds the survival limit offered by comprehensive medical treatment, as determined by the six-indices scoring system, orthotopic liver transplantation should be considered.

In conclusion, the six-indices scoring system provides a sensitive, specific, and simple analysis that may be helpful in selecting suitable medical treatment or liver transplantation in patients with ACLFB. A weakness of the study is that it was not a multi-centre comparative study. Nevertheless, our retrospective study can be regarded as a pilot study that has been completed in anticipation of a prospective multi-center cohort in the future, as previously described Hess *et al.* [22].

Acknowledgments

This work was supported by grants from the Natural Science Fund of Guangdong Province (No.10451008901004818), The National Natural Science Foundation of China (No. 30971356), The Technology Project Fund of Guangdong Province, China, No.2009B030801006, and the National Grand Program on Key Infectious Disease in the Treatment and Prevention of Infectious Diseases of AIDS and viral hepatitis, China, No. 2012ZX10002007-002.

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